

Amendments to the Specification:

Please replace title with the following amended title:

Manufacturing processes for ~~Se-alkylselenocysteine, Se-allylselenocysteine, Se-arylselenocysteine~~ Se-methyl-L-selenocysteine.

Please replace paragraph [0004] with the following amended paragraph:

[0004] The present patent describes efficient processes for the manufacture of L-Se-methylselenocysteine, D-Se-methylselenocysteine and DL-Se-methylselenocysteine: The structures of the referred materials are shown below; ~~Using the same chemical process, manufacture of Se-alkylselenocysteine, Se-allylselenocysteine, Se-arylselenocysteine is possible.~~

Please add the following new paragraphs after paragraph [0007]:

[0007.1] Grummon et al (US 3,678,067) describes a process for the synthesis of selenomethionine but involves the use of liquid ammonia and sodium. As pointed out already, such processes would be cumbersome to practice routinely

[0007.2] Chibata et al (US 4,401,820) teaches a process for the racemization of optically active amino acids using an aromatic aldehyde and aliphatic acid but does not teach or suggest the use of the process for selenium-containing amino acids.

Please replace paragraph [0010] with the following amended paragraph:

[0010] The invention sought to be patented relates to the synthesis of L-Se-methylselenocysteine (~~IIa~~) (Ia) by reaction with the salt of methylselenol (CH_3SeM where $\text{M} = \text{Na}, \text{K}$ etc) with L-Chloroalanine methyl ester hydrochloride (IIa) or with L-Chloroalanine hydrochloride (IIb) or with L-Chloroalanine (IIc).

Please replace paragraph [0011] with the following amended paragraph:

[0011] L-Chloroalanine methyl ester hydrochloride (IIa) was synthesized by a convenient method from the reaction of L-Serine methyl ester hydrochloride with phosphorous pentachloride in chloroform solution. The method of Walsh thionyl chloride in a solvent. The methods described earlier in the literature are not very convenient to use. For example, L-Serine methyl ester hydrochloride was reacted with phosphorous pentachloride in chloroform solution to give chloroalanine methyl ester hydrochloride (Walsh, C. T.; Schonbrunn, A.; Abeles, R. H.; J Biol Chem., 1971,246 (22), 6855-6866) is but one way of synthesizing L-Chloroalanine methyl ester hydrochloride (IIa). Alternatively other methods could be used. It is difficult to handle highly hygroscopic phosphorous pentachloride. The method described in the present patent uses more easily handled thionyl chloride. Then IIa is converted to L-Chloroalanine hydrochloride (IIb) by reaction with aqueous hydrochloric acid. L-Chloroalanine hydrochloride (IIb) could be neutralized with triethyl amine to form L-Chloroalanine (IIc). As mentioned, IIa, IIb and IIC were all convenient raw materials for L-Se-methyl selenocysteine.

Please replace paragraph [0013] with the following amended paragraph:

[0013] We also found that hypophosphorous acid could be used to cleave Se-Se- bond of dimethyldiselenide and the sodium salt of methylselenol was formed using sodium hydroxide. The methylselenide sodium thus generated was reacted with L-chloroalanine methyl ester hydrochloride (IIa), or L-chloroalanine hydrochloride (IIb) or L-chloroalanine (IIC) to get L-Se-methylselenocysteine. In extension of the above concept, one can use a dialkyldiselenide as a starting material to generate alkylselenide anion which can react with IIa, IIb or IIC to yield L-Se-alkylselenocysteine. ~~Similarly starting with diallyldiselenide and generating allyl selenide anion and further reacting with IIa or with IIb or with IIC, one can obtain L-Se-allylselenocysteine. These are straightforward extensions of the process patented in this application. Likewise diaryldiselenides could be used to generate arylselenol or arylselenide salts which could be used to produce Se-aryl selenocysteine.~~ In an analogous way, D-Se-methylselenocysteine (Ib) is obtained from D-Chloroalanine methyl ester hydrochloride (IIIa) or from D-Chloroalanine hydrochloride (IIIb) or from D-Chloroalanine (IIIC). These raw materials IIIa, IIIb and IIIC are obtainable from D-Serine methyl ester hydrochloride in a similar way described for the L-analogs.

Please replace paragraph [0014] with the following amended paragraph:

[0014] By similar processes, one can produce other D-Se-alkylselenocysteine ~~or D-Se-allylselenocysteine or D-Se-aryl selenocysteine.~~ Similarly in an analogous way DL-Se-

methylselenocysteine (Ic) is obtained from DL-Chloroalanine methyl ester hydrochloride (IVa) or from DL-Chloroalanine hydrochloride (IVb) or from DL-Chloroalanine (IVc). These raw materials are obtainable from DL-Serine methyl ester hydrochloride as described for the L-analogs.

Please replace paragraph [0015] with the following amended paragraph:

[0015] Extensions of the described processes to manufacture DL-Se-alkylselenocysteine or ~~DL-Se-allylselenocysteine or DL-arylselenocysteine~~ are possible.

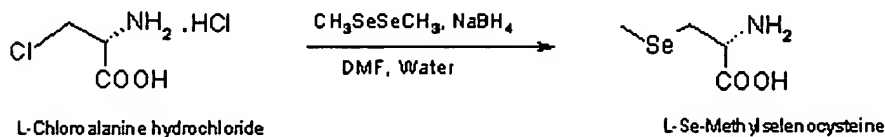
Please replace paragraph [0016] with the following amended paragraph:

[0016] Additionally DL-Se-methylselenocysteine (Ic) is also obtainable from L-Se-methylselenocysteine (Ia) or from D-Se-methylselenocysteine (Ib) by raceimization as the ~~Example 7~~ Example 4 described later in this embodiment will illustrate.

Please delete paragraphs [0020], [0021], and [0022].

Please replace paragraph [0023] with the following amended paragraph:

[0023] ~~Example 4~~ Example 1 **L-Se-Methyl Selenocysteine from L-Chloroalanine hydrochloride**



Dimethyldiselenide (50 g) in DMF (20 ml) was taken to get a clear solution. NaOH solution (24g in 100 ml water) was added under stirring. The mass was cooled to 5-10°C

and to this was added, portion-wise, solid sodium borohydride (6g) at $< 10^{\circ}\text{C}$. The reaction mixture was warmed to $40\text{-}45^{\circ}\text{C}$ and maintained for 2 hrs to get a clear colorless solution.

Please replace paragraph [0025] with the following amended paragraph:

[0025] The mass was concentrated under vacuum. Again 6N HCl (100 ml) was added to the mass and stirred well for 15 minutes. Again the mass was concentrated under vacuum to dryness. Methanol was added to the residue and stirred well for 30 mts. The product, L-Se-methylselenocysteine hydrochloride, dissolved in methanol leaving out the salts. The salts were removed by filtration. The pH of the filtrate was adjusted to 6-7 using triethylamine, TEA. The product L-Se-methylselenocysteine was filtered and washed with methanol (50 ml) and sucked dry. The product was further dried under vacuum.

Please replace paragraph [0028] with the following amended paragraph:

[0028] **Example 5 Example 2 L-Se-Methyl Selenocysteine from L-Chloroalanine methyl ester hydrochloride:** Dimethyldiselenide (56 g) in DMF (25 ml) was taken to get a clear solution. NaOH solution (34g in 150 ml water) was added under stirring. The mass was cooled to $5\text{-}10^{\circ}\text{C}$ and to this was added, portionwise, solid sodium borohydride (7g) at $< 10^{\circ}\text{C}$ over a period of 1 hr. The reaction mixture was warmed to $40\text{-}45^{\circ}\text{C}$ and maintained for 2 hrs to get a clear colorless solution.

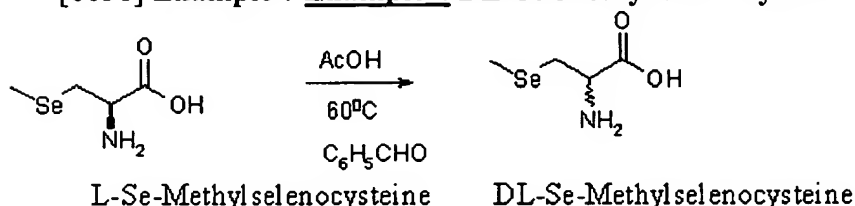
Please replace paragraph [0030] with the following amended paragraph:

[0030] **Example 6 Example 3 L-Se-methylselenocysteine from L-chloroalanine hydrochloride** (using hypophosphorous acid to reduce dimethyldiselenide to methane selenol): In a reaction flask equipped with a stirrer and condenser dimethylformamide (25ml) and dimethyldiselenide (55 g) were taken under an atmosphere of nitrogen. To this solution was added slowly hypophosphorous acid (32% solution, 73g) over a period of 30 mts. The reaction mixture was slowly heated to 70°C and maintained for 2 hrs. The reaction mixture was cooled to 10°C and sodium hydroxide solution (20g in 100 ml water) was added slowly. The mixture was stirred for another 30 mts at that temperature and L-chloroalanine hydrochloride (25 g in 100 ml water) was added over a period of 1 hr. The reaction mixture was stirred for another 1 hr

at RT and 1 hr at 40° C. After TLC indicated completion of the reaction, the reaction mixture was worked up as in Example 4. Yield : 10g

Please replace paragraph [0031] with the following amended paragraph:

[0031] ~~Example 7~~ **Example 4 DL-Se-Methyl selenocysteine**



A single-necked RB flask equipped with a magnetic stirring bar was charged with L-Methyl selenocysteine (0.5g), benzaldehyde(25 mg) and acetic acid (6 ml). The resulting suspension was heated to 60°C; After 15 minutes the reaction mixture became a clear solution. In another 20 minutes precipitation started. The mixture was stirred at this temperature for 2 hrs, then cooled to room temperature and filtered. The solid material was washed with ethanol thoroughly and dried in vacuo to afford 460 mg of white crystalline solid, DL-Se-Methylselenocysteine Yield: 460mg, 92%; MP: 189-190°C. The chiral HPLC of this material (Figure 1) indicated only two peaks of equal areas attesting to its racemic nature; No other peaks were detected; the peak with lower RT corresponded to L-Methyl selenocysteine.

Please replace paragraph [0032] with the following amended paragraph:

[0032] Convenient processes are described for the synthesis of L-Se-methylselenocysteine from chloroalanine derivatives. ~~Chloroalanine itself is produced in a new method involving Serine methyl ester hydrochloride and thionyl chloride.~~ The process is easily extendable to other selenium substituted amino acids. DL-Se-methylselenocysteine is easily obtained by an benzaldehyde-catalyzed racemization of L-Se-methylselenocysteine.